Chemistry 125 First Semester Final Examination
December 17, 2004 **Answer Key**

1. (31 minutes) **OMIT TWO OF THE FOLLOWING.** Describe briefly how **experimental** observation on **nine** of the following molecules played an important role in the **development of chemical theory in the indicated decade**.

a) Oxygen (1780s)
b) Salts of the fulminate anion, CNO^- (1820s)
c) Benzaldehyde C_6H_5CHO (1830s)
d) Cl_2 (1830s)
e) CH_4 (1850s)
f) Salicylic Acid (1860s)
g) Lactic Acid $CH_3CH(OH)COOH$ (1870s)
h) Cyclopropane (1880s)
i) Ethane (1930s)
j) NaRb-d-Tartrate (1940s)
k) 1,1,4,4-tetraphenylbutatriene (1970s)

(Each of the nine answers is worth 7 points. Note that specific experimental observations was asked for.)

a) During the 1780s Lavoisier and his contemporaries were studying the reaction of oxygen with various elements (such as S, P, C) and observing that the products (sulfuric, phosphoric, carbonic acids) were acidic or sharp to the taste. This gave rise to Lavoisier's theory that oxygen was the acidifying principle. He also used combustion with the oxygen in air as a means to analyse hydrocarbons by converting their hydrogen to water and their carbon to CO_2.

b) During the 1820s Justus Liebig was studying the salts of (explosive) fulminic acid (HCNO), while Friedrich Wöhler was studying salts of cyanic acid (HNCO). Corresponding salts had the same elemental composition, showing that there was more to a substance than its elemental composition. This observation supported the concept of isomerism..

c) Benzaldehyde (oil of bitter almonds) was transformed by Liebig and Wöhler, into a series of compounds (benzoic acid, benzoyl chloride, benzamide, etc.) each of which included C_6H_5O in its analysis. This suggested that there was a permanent "compound radical" which survived reaction and could play the same role in organic chemistry that elements played in inorganic chemistry – the radical theory.

d) During the 1830 Dumas observed that reaction with elemental chlorine in the presence of light converted acetic acid into chloro, dichloro- and trichloroactetic acids. This meant that the "acetyl" radical was not impervious to transformation and suggested the substitution, or "type" theory of organic chemistry.

e) Methane (or marsh gas) was identified as a type because it could be converted to chloro-, dichloro-, trichloro-, tetrachloro methane. Couper noted that these substitutions suggested that carbon was central to such compounds (had the group of hydrogens been central, one could have imagined substituting the carbon by chlorine to give H4Cl4). This suggested the idea of bonds and valence, specifically the tetravalence of carbon.

f) In the 1860s a number of substitution reactions were carried out involving salicylic acid and its two isomers (which were known as hydroxybenzoic and parahydroxybenzoic acids). For example, replacing the hydroxyl groups (or the carboxyl groups) of the three isomers by H yielded a single benzoic acid (or phenol). Koerner was able to use such relationships among identical or isomeric products to demonstrate that the six positions for hydrogen in benzene are equivalent, and ultimately to establish position in chemical structures.

g) During the 1870s Wislicenus established that the isomeric acids isolated from meat and milk had the same constitution showing that there was more to a substance than its constitution. Van't Hoff explained this isomerism in terms of the tetrahedral carbon bearing four different groups and thus established the concept of chemical structure in 3D space.

h) In the 1880s Baeyer noted that, unlike most hydrocarbons lacking double bonds, cyclopropane reacts readily with HBr. He attributed the reactivity to a state of strain in the ring owing to the departure of the C-C-C bond angles from their favored value of 109.5°. This could be considered the origin of mechanical models for organic molecules.

i) In the 1930s Pitzer interpreted the heat capacity of ethane to establish a 3 kcal/mole barrier to rotation about the H_3C-CH_3 single bond. This launched the study of torsional energy and conformational analysis.

j) In the 1940s, Bijvoet used x-ray diffraction (using a special effect called "anomalous dispersion") to determine the exact arrangement in space of the atoms in sodium rubidium tartrate, and thus establish the absolute configuration of a stereogenic carbon atom.

k) In the 1970s Leiserowitz and Berkovitch-Yellin determined the electron difference density in tetraphenylbutatriene showing the expected extension of pi bonds and thus establishing the reliability of this technique for studying bonding electron density.

2. (3 min) Give a **chemically relevant** example for each of the following:

A force of the form $F \propto 1/r^2$

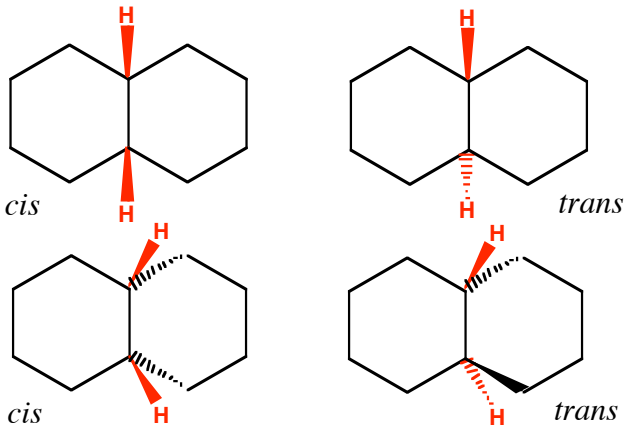
This is the form of Coulomb's Law for electrostatic interaction among electrons and nuclei. This is the fundamental potential for all chemical interaction. The interaction of ions also is governed by Coulomb's Law

A force of the form $F \propto |x|$

This is the form of Hooke's Law (*ut tensio sic vis*) which is a reasonable approximation for the force between bonded atoms for small displacement (x) from the equilibrium bond distance. [I messed up in writing the question and said x^2 instead of |x|. The potential energy is proportional to x^2, but the force is proportional to x. For purposes of the test it is fortunate that few students caught the error. Those who did were given full credit.]

3. **Decalin** ($C_{10}H_{18}$,) occurs as two configurational isomers, called *cis* and *trans*, **without any substituents**.

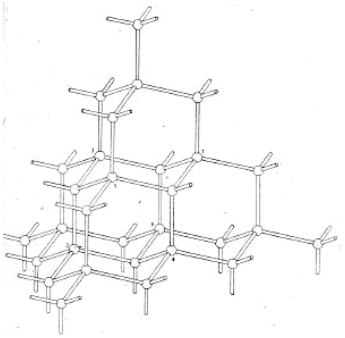
a) (2 min) **Modify** the two structures so as to show the configurational difference between these two unsubstituted isomers unambiguously.



The standard way to draw the decalin isomers is shown in the upper pair of structures, and it is unambiguous in showing the positions of the hydrogen atoms with respect to the mean plane of the carbon atoms.

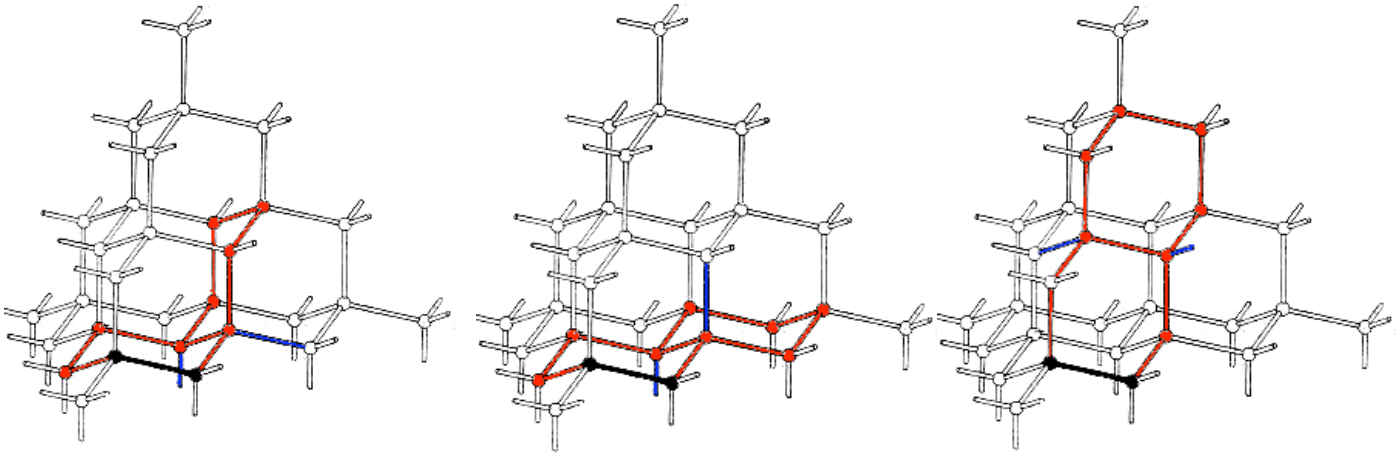
The second pair of structures uses dashes and wedges to show the tetrahedral carbons a little more accurately, but is rarely used for this kind of structure, because it does no better than the first pair in showing the conformation of the rings.

b) (5 min) The figure at the right is from a paper published in 1918. State what the figure shows, and explain briefly how this paper relates to the publications of Hermann Sachse in the early 1890s.



The figure (from a paper by Ernst Mohr) does a good job of showing the arrangement of carbon atoms in the crystal lattice of diamond (as determined by x-ray diffraction by the Braggs). In the early 1890s Sachse had explained that carbon atoms in a six-membered ring could have tetrahedral bond angles of 109.5°, if the ring were puckered, rather than flat as proposed by Baeyer. This structure shows carbon atoms in just this sort of arrangement.

c) (5 min) Here are three copies of the figure above with one bond darkened. **Darken 10 more bonds in each of the first two figures** to show C-C bonds of idealized conformations for *cis*- and *trans*-decalin. (The third is a spare).



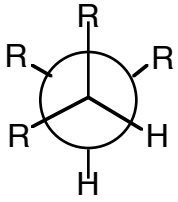
cis-decalin *trans*-decalin (*trans*-decalin)

[The red lines in the figures above are correctly darkened, and blue lines have been filled in to show the arrangement of the C-H bonds from Question 3a. Note that there are numerous ways to pick out each isomer in the shown portion of the diamond lattice. Two different ways are shown for *trans*-decalin.]

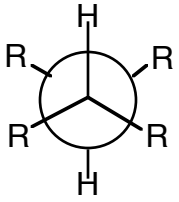
d) (3 min) Draw **Newman projections** to show the arrangement of substituents on the **central pair of carbons** of ***cis*- and *trans*-decalin**. (Use H for hydrogen and R for CH_2)

[Note that the two C-H bonds are gauche in *cis*-decalin and *anti* in trans-decalin.]

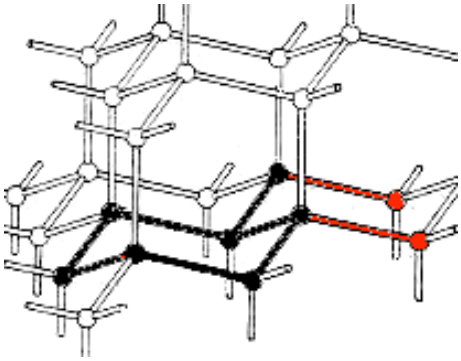
Cis

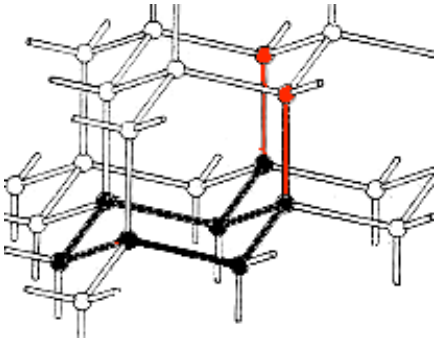


Trans



e) (5 min) Use your knowledge of the energy difference between the conformational isomers of normal **butane** to **estimate the energy difference between *cis*- and *trans*-decalin.** (explain briefly)





The relevant difference between the conformations is shown by the red bonds in the figures above. In the *trans* isomer (left) the red bonds are involved in 3 *anti* and 2 *gauche* butane structures with the black bonds. In the *cis* isomer (right) the red bonds are involved in 5 *gauche* butane structures with the black bonds. Since 3 *anti* conformations become *gauche*, one might expect the *cis* isomer to be higher in energy than the *trans* isomer by 3 times the energy difference between *gauche* and *anti* butane. Since this difference is 0.9 kcal/mole, the difference between the decalin isomers might be expected to be 2.7 kcal/mole. [Note in the next question that the experimental difference is 2.6 (±0.3) kcal/mole – not a bad guess!]

f) (5 min) The experimental **heat of formation** of *cis*-decalin is –52.5 (±0.2) kcal/mole; that of *trans*-decalin is –55.1 (±0.2). Explain what **experiments** were necessary to determine these numbers.

1) Measure the heat of combustion of the two decalins
2) Measure the heat of combustion of graphite
3) Measure the heat of combustion of hydrogen gas

The difference between the heat of combustion of the organic compounds and that of the corresponding quantities of the elements is the heat of formation.

g) (8 min) Chem3D was used to construct **"idealized"** structures for the decalins (**normal bond distances and angles**). Then it was used to minimize the energy of each isomer. The table below shows the total strain energy (kcal/mole) for idealized *cis* isomer and for the energy-minimized versions of both *cis* and *trans* isomers, followed by the contributions to these energies.

Decalin Model	"Source" of Energy → Total Energy	non-1,4-va der Waals	Stretch-Bend Interaction	Bond Stretch	Bond Angl Bending	Torsion	1,4-van de Waals
idealized *cis*	26.3	9.0	0.0	0.0	0.0	5.3	11.9
minimized *cis*	14.1	-2.4	0.2	0.8	1.4	5.6	8.5
minimized *trans*	11.4	-2.6	0.2	0.7	0.7	4.2	8.3

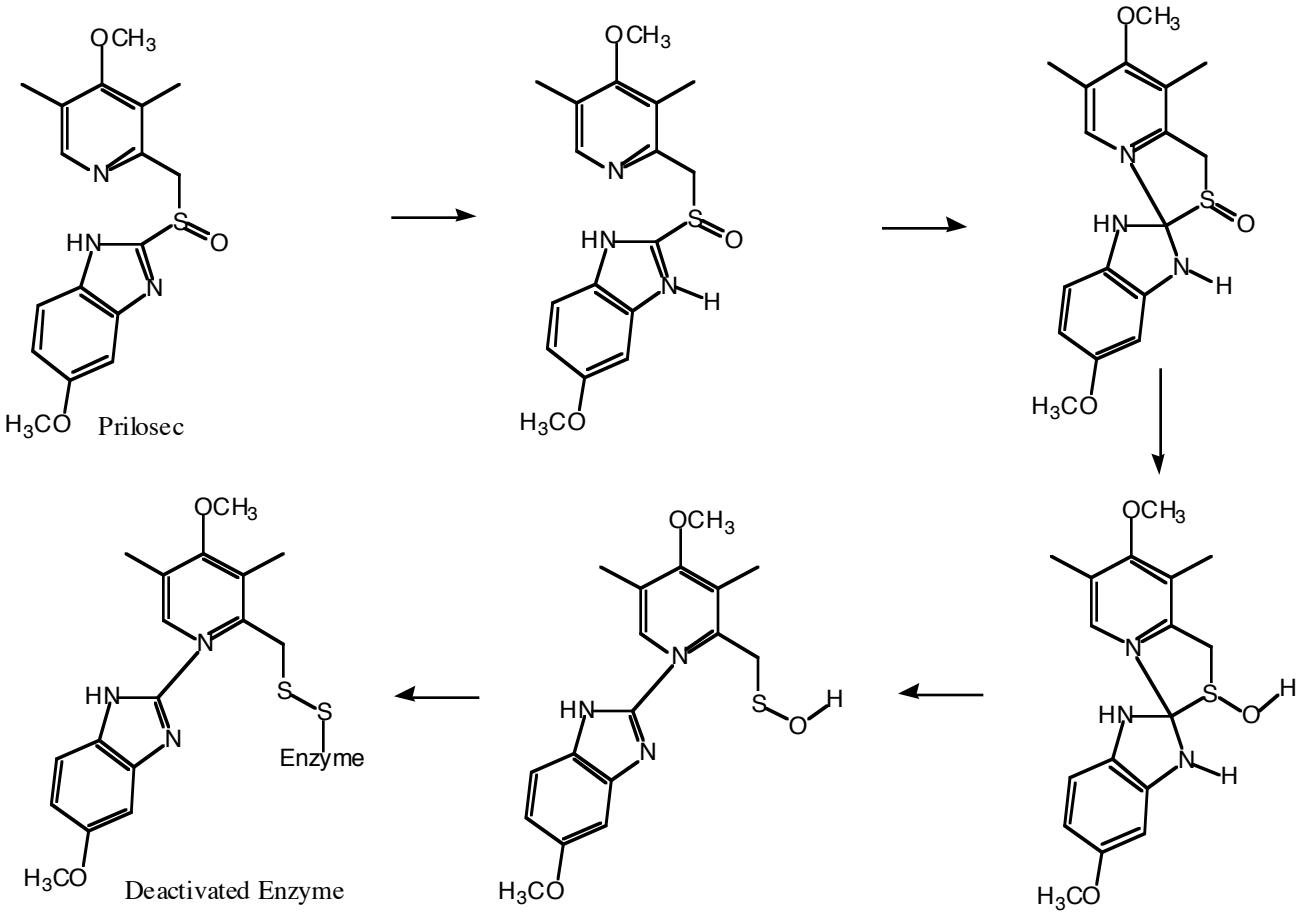
The column for bond stretching energies is labeled. **Complete the top row** by entering an appropriate label for each of the other columns.

Comment very briefly on the **magnitude and direction** of each change in component energy **between the second and third rows** (*i.e.* what happens to minimize the energy of *cis*-decalin, and why?).

Since the initial "idealized" structure has no stretch, bend, or stretch-bend strain, the initial strain to be relieved is due to van der Waals and torsion. The principal accommodation is bond bending (with a lesser amount of "stiffer" bond stretching). Modest motion does not change the torsional energy very much. "Relaxation" of the gauche CH_2 interactions reduces the van der Waals energies, particularly the unfavorable non-1,4 component due to H atoms attached to the gauche carbon atoms. Note that the net non-1,4-van der Waals energy can be favorable, because of the attraction between distant groups, while 1,4 must be net unfavorable.

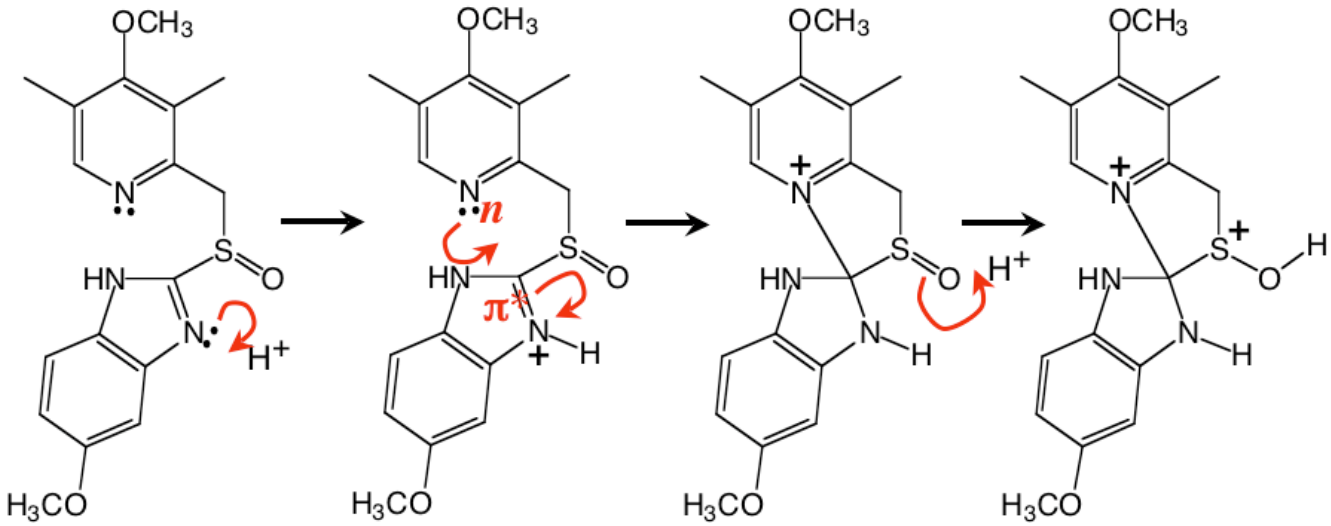
4. **Prilosec**

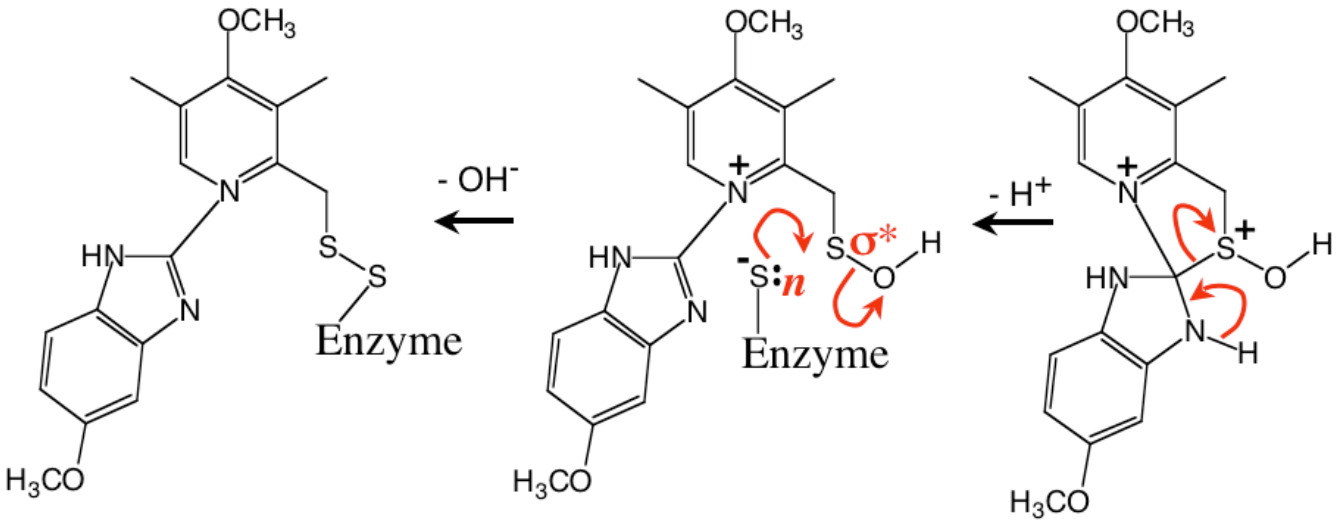
a) (13 min) The following partial scheme shows how the proton pump inhibitor prilosec may function in cells of the stomach lining to tie up the enzyme that turns on production of HCl. **Complete the scheme** by adding other necessary **reagents, charges, relevant unshared pairs, and carefully drawn curved arrows** to show the making or breaking of each bond that changes.



A Powerpoint animated version of the following scheme was given in the lecture of 11/19/2004

Remember that each curved arrow should originate where the electron density is high in an unusually high HOMO and should end where a new bond is to be formed because of the overlap of this HOMO with an unusually low LUMO.





b) (4 min) Explain why one N is more reactive that the other two in the first step of the scheme above.

The unshared pairs that are shown explicitly in the first structure involve sp^2 hybridization, so one might think they would be lower in energy that the unshared pair on the N that bears an H, however this latter N is like the N of an amide, because its unshared pair mixes with the π^* orbital of the adjacent C=N group (analogous to the C=O group of an amide). This mixing both lowers the p-orbital energy of the N substantially (as in an amide) and shifts electron density to the p orbital of the double bonded N. The unusually high e-density on the double bonded N makes its unshared pair unusually high in energy, so that this is the N that is protonated most easily in the first step of the reaction. (Similarly an amide is protonated more easily on O than N, although one might naively have expected the opposite.)

c) (4 min) Explain why one C=N group is more reactive that the other in the second step of the scheme above.

The lower , protonated C=N group has a lowered LUMO because of the positive charge on its N.

d) (4 min) Explain why the S-O bond is reactive in the last step of the scheme above.

There are two reasons:

First, the bond involves two relatively electronegative elements and thus an unusually low LUMO (same reason the R-O-O-R peroxide bond and the Cl-Cl bond are readily attacked by high HOMO "nucleophiles"). [Actually the S atoms has the same numerical electronegativity as carbon, but still it is unusually electronegative for a second-row element, and second row elements have reduced overlap with first row elements – which explains having an unusually low LUMO.]

Second,the S-O bond involves two atoms with two unshared pairs apiece (four unshared pairs altogether). These unshared pairs can be considered to occupy π^* antibonding as well as π bonding MOs, and thus to weaken the S-O bond. The same effect is seen in the dihalogen molecules (and in peroxides).

e) (3 min) When it was proposed to prepare esomeprazole as a potential drug, there was concern that it would be no different from racemic prilosec, because of the mechanism above. Explain.

Although the first five steps in the scheme involve chiral structures (trivalent S is the chiral center), which might react differently with single enantiomer biological molecules, the R-S-O-H which deactivates the enzyme is achiral – the same intermediate would be formed from racemic as from resolved omeprazole. Furthermore, the steps that lead up to the reactive R-S-O-H intermediate do not require any enzyme catalyst, just H^+, so there is no reason to think that one enantiomer would form the intermediate more readily than the other.

f) (9 min) Three completely different techniques were used to prepare esomeprazole (Nexium) as a single enantiomer. Explain each technique being sure to **say what initial substance** provided the bias that led to a single enantiomer.

i) For preparing a few mg for testing configurational stability

This small scale separationn was achieved by chromatography using a chiral resolved column packing. The packing was made from natural cellulose, which is a single enantiomer. [The cellulose had been modified by converting its OH groups to O-CO-NHPh groups.]

ii) For preparing some hundreds of mg for biological testing

This separation was achieved by converting the omeprazole to an ester with natural (S)-mandelic acid [Ph–CHOH–COOH], separating the diastereomeric esters by crystallization, and converting the desired ester back into omeprazole by removeing the mandelate group.

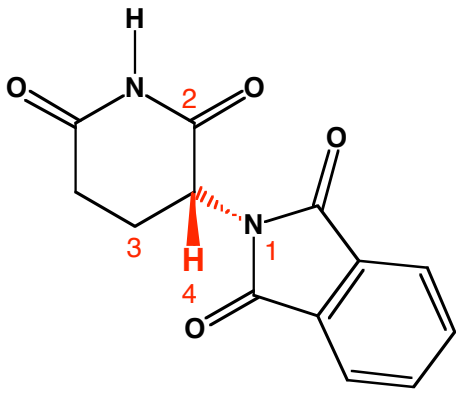
iii) For preparing large quantities for sale as a drug

For large-scale production of the drug, a single enantiomer was prepared by adding the oxygen to sulfur using a titanium catalyst that incorporated a derivative of d-tartaric acid [actually diethyltartrate].

[For further details see slides 9-11 of the Powerpoint lecture referred to above]

5. Thalidomide

This drug has the structure shown with two "imide" groups (O=C-NH-C=O).



a) (5 min) **List factors** that would favor a coplanar structure for the three bonds to N in an imide, **and** those that would favor a pyramidal structure, and **explain which** structure you expect to occur, perhaps mentioning an analogous compound.

FAVOR COPLANARITY:

Hybridization of single bonds (better overlap with planar sp^2 than with pyramidal sp^3 hybrids).

Overlap between lone pair orbital of N and π^* orbitals of C=O groups.

FAVOR PYRAMIDAL NITROGEN:

Lower energy (more s-character) of N orbital that is solely responsible for the unshared pair of electrons (rather than for one of the two electrons in a bonding orbital shared with C or H)

The planar structure should be favored because there are two C=O groups to stabilize the unshared electron pair on planar nitrogen, and even with a single such C=O group the N of an amide is known to be planar.

b) (4 min) Explain how you might use infrared spectroscopy to test whether the H attached to N lies in or out of the local molecular plane in thalidomide.

If the structure favored planarity, out-of-plane vibration of the H atom would involve a single-minimum potential energy. If it were pyramidal, the potential would involve a double minimum. Thus it is possible that, as in NH_3, the double minimum would involve a splitting of the corresponding infrared peak into two closely spaced peaks, while the single minimum would give a single unsplit IR peak.

c) (5 min) Modify the structure shown above so that it unambiguously represents (R)-thalidomide. (Explain your thinking for partial credit in case of error)

See red additions to the formula above. The numbers rank the substituents on the stereogenic carbon in order of decreasing priority.

Researchers who studied interconversion of the enantiomers of thalidomide in human blood reported that the rate for R→S is 0.17/hour, while that for S→R is 0.12/hour.

d) (2 min) Why are these rates particularly interesting for medicine?

If the enantiomers interconvert rapidly *in vivo* (in the body), it makes no difference which enantiomer is administered as a drug, since both will quickly be present in the bloodstream. [unless the drug is eliminated from the body faster than racemization occurs]

e) (4 min) The faster rate for R→S suggests that there should be about 1.4 times as much S as R at equilibrium. **Circle** the most likely value for the excess energy of R over S (in kcal/mole)in the following list: 0.01 , 0.05 , 0.2 , 0.8 , 3 , 8 and **use an equation to explain** your choice.

$K = 1.4 = 10^{3/4\ \Delta H}$

So the question is what power of 10 is 1.4. One could do this with a calculator, but the cube root of 10 is a little greater that 2 and the square root of 2 is 1.4, so 1.4 is about 10 to the 1/3 * 1/2 = 1/6 power.

Thus $3/4\ \Delta H \approx 1/6$

Or $\Delta H \approx 1/6 * 4/3 = 2/9$

Thus 0.2 (2/10) is the closest value in the list. (The precise value is 0.195)

f) (3 min) **Explain** whether it is conceivable for the R and S isomers to differ in energy in and out of the body.

Within the body enantiomeric molecules may be associated with proteins or other single-enantiomer biological molecules, forming diastereomeric complexes of different energy. Thus enantiomers could indeed have different energy in the body, just as they would have different energies in a resolved chiral solvent. Out of the body, in the absence of single-enantiomer substances, they must have identical energies, because they are mirror images.

6. (6 min) Define each of the following terms:

Anti-bonding Orbital

An anti-bonding molecular orbital is the unfavorable combination of component orbitals from two fragments. The energy of electrons in such an orbital will thus fall if the two fragments dissociate from one another. Occupancy of an anti-bonding orbital with tend to cause the molecule to dissociate.

Bürgi-Dunitz Angle

The angle at which a nitrogen (or other HOMO atom) prefers to approach the LUMO of the C=O group in forming a new bond. Comparison of many x-ray structures involving N: near to C=O shows the preferred N···C=O angle to be about 110°.

Correlation Energy

The overestimation of energy that is made by using a self-consistent-field product wave function, which ignores the stabilization that results from electrons correlating their motions to keep away from one another.

7. (2 min) What is typically given, and what to find, in a chemical quantum mechanics problem?

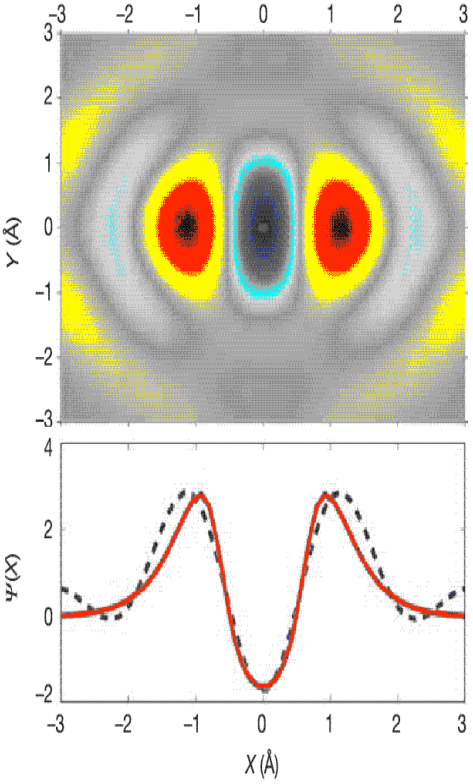
GIVEN: Mass and charge (*i.e.* potential energy law) of particles.

TO FIND: Wave Functions and their associated energies.

8. This week's issue of *Nature* (vol. 432, p. 867) reports a surprising new experiment that is said to determine the **shape and relative signs(!) of a single molecular orbital**. The figure on the right shows a slice through an orbital of the $\mathbf{N_2}$ molecule as measured experimentally in this way. To interpret the Å scale, **NOTE that the N-N distance in N_2 is 1.09Å**

[The original figure is colored with the dark central blob shades of blue and the flanking "eyes" shades of red to denote the wave function's negative and positive signs, respectively. The lighter surrounding features are probably insignificant beacause of experimental error.]

The lower graph, with the same horizontal scale, plots the MO wave function ψ along the Y = 0 line of the upper graph. The dashed line is experimental, and the solid line is the result of an MO calculation.



a) (4 min) How does this picture differ from what is available from **x-ray** diffraction? (Ignore the difficulty of preparing a crystal of N_2).

X-ray diffraction shows the total electron density, that is the sum of the squares of all of the occupied orbitals. This picture shows the *wave function* (with positive and negative regions) of a single electron orbital.

b) (2 min) What **atomic orbitals** of nitrogen seem to dominate in making up this MO?

Since the nitrogen nuclei are about 1 Å apart, they lie near the nodes of the MO, thus the atomic orbitals on each nitrogen must have a large 2p component. The MO may be thought of as the favorable combinatior of sp hybridized lone pair atomic orbitals on each nitrogen each pointing away from the center of the molecule. The HOMO of N_2 is a sigma, not a pi MO.

c) (4 min) At the extremes of the lower plot, the calculated (solid) wave function seems to approach Ψ=0 exponentially, while the experimental (dashed) curve has extra wiggles. Explain which behavior makes more sense in terms of reasonable kinetic and potential energy for an electron in this orbital.

Far from the nuclei, where the total energy of the electron is higher than the kinetic energy of a bound electron, the wave function must approach psi=0 asymptotically. If it ever slopes away from the psi=0 baseline, it will be unsatisfactory, since, in the classically forbidden region, it must keep curving away from the baseline and diverge to infinity. Thus the extra wiggles in the experimentally determined function must be artifacts due to experimental error.

d) (4 min) This orbital is said to be the HOMO of N_2. If so, **explain where in the top figure** you would expect H^+ to add to the molecule, **and** whether protonation should make the N–N distance **longer or shorter**.

H^+ should attack from the right (or the left) along the N-N axis to achieve good overlap with a single lobe of the HOMO. Attacking from any other angle would entail overlap with lobes of different color (sign) and thus both bonding and antibonding components (partial or complete orthogonality).

This HOMO is bonding between the two N atoms (favorable "blue" overlap between the nuclei), so that removing electron density from this region to share with the H^+ should weaken and lengthen the N-N bond.